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Late primary angioplasty (beyond 12 h): are we sure it should be avoided?

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Optimal management for patients with ST-segment elevation myocardial infarction (STEMI) who arrive at a hospital late remains uncertain since evidence and real-world data are limited. Patients who present late with a STEMI are a heterogeneous population, and the clinical decision regarding percutaneous coronary intervention (PCI) should not be the same for all. One randomized clinical trial, multiple mechanistic studies, and contemporary registries suggest a presumed benefit for a prompt restoration of coronary flow even in late presenting STEMI. Crucial elements in decision-making are the presence of haemodynamic or electrical instability, and ongoing ischaemic signs or symptoms to tip the scales toward PCI. Among clinically stable, late-presenting patients, myocardial viability assessment and functional testing can identify yet another subgroup that may benefit from late PCI

Although the rate of late presentations among patients with ST-segment elevation myocardial infarction (STEMI) appears to have decreased over the decades, ~10–12% of patients with STEMI present later than 12 h after symptom onset.[1–4] In a recent, large, nationwide, prospective Korean registry, STEMI late presenters (12–48 h of symptom onset) had remarkably worse clinical outcomes up to 3 years than early presenters, whereas presentation at ≥12 h of symptom onset was not independently associated with increased mortality following STEMI. Inverse steep differences in the use of percutaneous coronary intervention (PCI) and mortality rates were found between early (<12 h) and late (12–48 h) presentations indicating that the practice pattern of interventional procedures might affect the clinical outcomes of STEMI late presenters.[5] Thus, optimal management for patients with STEMI who arrive at a hospital late remains uncertain and the boundary between 'timely' and 'late' presentation in STEMI and the appropriateness of PCI in patients presenting late after the onset of symptoms, continue to be challenged by the most recent published data. Additionally, the 12-h limit is originally based on a combination of fibrinolysis being unable to reduce mortality in late-presenting STEMI patients[6,7] and on animal models reporting loss of all jeopardized myocardium before 12 h of coronary occlusion.[8] However, data on the 12-h limit is inadequate in the modern era of primary PCI.

Potential benefits of late reperfusion of infarcted myocardium

Since the initial reports of a beneficial effect of reperfusion therapy in the management of STEMI, the open artery hypothesis and the benefits of timely reperfusion have been confirmed in numerous clinical trials investigating either pharmacological or mechanical reperfusion with PCI.[9] However, while the 'early' open artery hypothesis has been consistently confirmed, the 'late' open artery hypothesis (i.e., reperfusion of an occluded infarct-related artery at a time too late for myocardial salvage and in patients without continuous symptoms) has been controversial for years. The rationale is that patency of the infarct vessel can improve left ventricular systolic function, and prevent ventricular remodelling and the late development of arrhythmias.

The mechanism by which myocardial cells escape irreversible death despite hours of decreased oxygen supply is not fully elucidated. In addition to collateral formation as a

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mechanism for preserving myocardial viability, the hazy nature of acute myocardial infarction time could also be important. Initial coronary occlusion is generally equated with symptom onset in clinical trials and registries. Furthermore, the time from symptom onset to hospital presentation is generally equated with a period of continuous coronary occlusion. These equations are likely wrong: plaque instability is a dynamic process and not easily fixed at a single time.[10] Thrombus propagation at the onset of an acute coronary syndrome may result in dynamic coronary occlusion and reperfusion with consequent ischaemic preconditioning and a resulting delay of progression to irreversible myocardial injury.

Many other possible mechanisms by which an open infarct-related artery could confer benefit in ways other than by salvaging ischaemic myocardium have been proposed.[11] For instance, when the importance of the early inflammatory response needed to initiate infarct scar formation is considered, restoration of blood flow and allowing an influx of inflammatory cells into the infarct may improve healing of the infarcted tissue and prevent ventricular remodelling.[12] In addition, an open, blood-filled infarct-related artery and vascular bed may provide a supporting scaffold that helps maintain the structural integrity of the necrotic myocardium and limits infarct expansion and ventricular remodelling.[13] Another proposed mechanism suggests that late reperfusion elicits intra-myocardial haemorrhage, oedema, and contraction band necrosis, within which sarcolemmal tubes persist and prevent collapse of the necrotic tissue.[14] Late revascularization of 'hibernating' myocardium present within the peri-infarct region is also a possible benefit of a patent infarct-related artery.[15] Collagen turnover is reportedly more pronounced in patients with an occluded infarct-related artery, and thus prevention of interstitial collagen turnover may be another beneficial effect.[16] Finally, a recent study reported a significantly higher rate of apoptosis among cardiomyocytes in patients with persistent occlusion of the infarct-related artery.[17] This increased apoptosis was apparent well beyond the acute phase of MI, and those investigators proposed that late reperfusion might inhibit the apoptotic loss of salvaged cardiomyocytes, thereby preventing the progression of heart failure.

Myocardial salvage from percutaneous coronary intervention in late presenting ST-segment elevation myocardial infarction

The potential of myocardial salvage even in late presenters treated with PCI has been investigated in several studies using single-photon emission computed tomography or cardiac magnetic resonance (CMR) imaging.[18-20] Busk *et al.*[18] analysed the results of single-photon emission computed tomography performed in 396 STEMI patients and demonstrated that late presenters (12–72 h of symptom onset) had a lower salvage index (proportion of salvaged area at risk) than early presenters [48% (IQR 23–73%) vs. 57% (IQR 42–86%); $P = 0.003$]: however, substantial salvage (>50% of area at risk) was observed in 41% of late presenters despite total infarct-artery occlusion. They also found that final infarct size and salvage index correlated weakly with symptom duration (R^2-value <0.10). Stiermaier *et al.*[19] compared two cohorts [early (<12 h of symptom onset) and late (12–48 h of symptom onset) presentation] involving 186 STEMI patients matched for the area at risk by cardiac magnetic resonance imaging and demonstrated that myocardial salvage (area at risk minus infarct size) significantly decreased in late presenters as compared with that in early presenters. Nevertheless, >25% of the area at risk could be salvaged in late presenters. Nepper-Christensen *et al.*[20] had recently analysed 865 STEMI patients (807 patients presenting at <12 h and 58 patients presenting at 12–72 h) who underwent cardiac magnetic resonance imaging just after index PCI and 3 months later; they reported that 65% of late-presenting patients achieved substantial myocardial salvage ≥0.50.

Progress in the cardiac magnetic resonance technology and availability may eventually lead to CMR characterization of myocardial status before primary PCI in patients presenting late and could move the treatment of late presentation acute STEMI toward a more personalized approach.

Evidence on the percutaneous coronary intervention strategy for late ST-segment elevation myocardial infarction

Schömig *et al.*[21] performed the first randomized controlled trial involving 365 STEMI patients from 2001 to 2004 and showed that an invasive strategy based on coronary stenting with adjunctive abciximab use reduced the infarct size and the 4-year mortality in STEMI patients without persistent symptoms who presented at 12–48 h after symptom onset.[21,22] On the contrary, establishing flow in the epicardial coronary artery with PCI in very late presenters (3-28 days) in the Occluded Artery Trial (OAT) did not improve mortality or left ventricle ejection fraction during 4-year follow-up compared with medical therapy.[23] However, BRAVE-2 and OAT are hardly comparable, as the patients underwent angioplasty at 2 very different time points from symptom onset (a median of <24 h vs. 8 days). Imaging and clinical studies have reported results similar to BRAVE-2, with a reduction in myocardial damage or improved clinical outcome after primary PCI in patients with STEMI presenting 12–72 h after symptom onset. Gierlotka *et al.*[24] evaluated 2036 STEMI patients from the Polish registry who presented at 12–24 h of symptom onset and observed that the invasive approach (performance of coronary angiography at 12–24 h from symptom onset) was significantly associated with better 12-month clinical outcomes than the conservative approach (non-invasive treatment or performance of coronary angiography at >24 h from symptom onset) after multivariable adjustment and propensity score matching, with a relative risk of 0.73. These clinical findings have been further supported by mechanistic SPECT and cardiac magnetic resonance imaging registry studies comparing early vs. late STEMI presenters; while myocardial salvage is less with late presenters than early presenters, substantial myocardial salvage may be observed when PCI is performed at the 12–48 h outer edge of time limits

for STEMI PCI.[18-20] Based on these studies, the 2017 European guidelines advocate the performance of primary PCI for unstable patients presenting at 12–24 h of symptom onset exhibiting signs of ongoing ischaemia (Class of Recommendation: I; Level of Evidence: C) and suggest the use of routine primary PCI for stable STEMI patients presenting at 12–48 h of symptom onset (Class of Recommendation: IIa; Level of Evidence: B).[25]

Conclusions

Patients who present late with an acute MI are a heterogeneous population, and the clinical decision regarding PCI should not be the same for all. Late presenters are different than early presenters. Most importantly, late presentation is associated with increased death. Given that two-thirds of late presenters are transfers from non-PCI centres and represent a high-risk group for death, further system-wide approaches might focus on bringing clarity to recommendations for best practices among late-presenting STEMI patients. In the treatment of late-comers with STEMI, clinical evaluation and risk stratification represent paramount factors helping in decision-making for the best therapeutic management. One randomized clinical trial, multiple mechanistic studies, and now contemporary registries seem to point in a single direction:[18,20-22] at the outer edge of acute myocardial infarction time, there is a presumed benefit for a prompt restoration of coronary flow.

Crucial elements in decision making are the presence of haemodynamic or electrical instability, and ongoing ischaemic signs or symptoms to tip the scales toward PCI. Among clinically stable, late-presenting patients, myocardial viability assessment and functional testing can identify yet another subgroup that may benefit from late PCI. Accordingly, as recommended and endorsed by the current guidelines, patients who are still early in the course of STEMI (12–48 h) should undergo PCI. Those beyond 48 h with evidence of silent ischaemia or viability should also undergo PCI. Patients who are truly stable and asymptomatic beyond 48 h from symptom onset, with no evidence of silent ischaemia or viability, can safely be treated with medical therapy.

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References

1. Schömig A, Ndrepepa G, Kastrati A. Late myocardial salvage: time to recognise its reality in the reperfusion therapy of acute myocardial infarction. *Eur Heart J* 2006;**27**:1900–1907.
2. Cerrato E, Forno D, Ferro S, Chinaglia A. Characteristics, in-hospital management and outcome of late acute ST-elevation myocardial infarction presenters. *J Cardiovasc Med* 2017;**18**:567–571.
3. McNair PW, Bilchick KC, Keeley EC. Very late presentation in ST elevation myocardial infarction: predictors and long-term mortality. *Int J Cardiol Heart Vasc* 2019;**22**:156–159.
4. Roberto M, Radovanovic D, de Benedetti E, Biasco L, Halasz G, Quagliana A, Erne P, Rickli H, Pedrazzini G, Moccetti M. Temporal trends in latecomer STEMI patients: insights from the AMIS Plus registry 1997- 2017. *Rev Esp Cardiol* 2020;**73**:741–748.
5. Cho KH, Han X, Ahn JH, Hyun DY, Kim MC, Sim DS, Hong YJ, Kim JH, Ahn Y, Hwang JY, Oh SK, Cha KS, Choi CU, Hwang K-K, Gwon HC, Jeong MH. Long-term outcomes of patients with late presentation of st-segment elevation myocardial infarction. *J Am Coll Cardiol* 2021;**77**:1859–1870.
6. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6-24 hours after onset of acute myocardial infarction. *Lancet* 1993;**342**:759–766.
7. EMERAS (Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet* 1993;**342**:767–772.
8. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischaemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;**56**:786–794.
9. Boersma E; for the Primary Coronary Angioplasty vs, Thrombolysis Group. Does time matter? A pooled analysis of randomised clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 2006;**27**:779–788.
10. Rittersma SZH, van der Wal AC, Koch KT, Piek JJ, Henriques JPS, Mulder KJ, Ploegmakers JPHM, Meesterman M, de Winter RJ. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. *Circulation* 2005;**111**:1160–1165.
11. Kim CB, Braunwald E. Potential benefits of late reperfusion of infarcted myocardium. The open artery hypothesis. *Circulation* 1993;**88**:2426–2436.
12. Hammerman H, Schoen FJ, Braunwald E, Kloner RA. Drug-induced expansion of infarct: morphologic and functional correlations. *Circulation* 1984;**69**:611–617.
13. Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. *N Engl J Med* 1988;**319**:80–86.
14. Pirzada FA, Weiner JM, Hood WB Jr. Experimental myocardial infarction. Accelerated myocardial stiffening related to coronary reperfusion following ischaemia. *Chest* 1978;**74**:190–195.
15. Kloner RA. Coronary angioplasty: a treatment option for left ventricular remodelling after myocardial infarction? *J Am Coll Cardiol* 1992;**20**:314–316.
16. Uusimaa P, Risteli J, Niemelä M, Lumme J, IkäHeimo M, Jounela A, Peuhkurinen K, Collagen scar formation after acute myocardial infarction: relationships to infarct size, left ventricular function, and coronary artery patency. *Circulation* 1997;**96**:2565–2572.
17. Abbate A, Bussani R, Biondi-Zoccai GGL, Rossiello R, Silvestri F, Baldi F, Biasucci LM, Baldi A. Persistent infarct-related artery occlusion is associated with an increased myocardial apoptosis at post-mortem examination in humans late after an acute myocardial infarction. *Circulation* 2002;**106**:1051–1054.
18. Busk M, Kaltoft A, Nielsen SS, et al. Infarct size and myocardial salvage after primary angioplasty in patients presenting with symptoms for <12 h vs. 12–72 h. *Eur Heart J* 2009;**30**:1322–1330.
19. Stiermaier T, Eitel I, de Waha S, Pöss J, Fuernau G, Thiele H, Desch S. Myocardial salvage after primary percutaneous coronary intervention in patients with ST elevation myocardial infarction presenting early versus late after symptom onset. *Int J Cardiovasc Imaging* 2017;**33**:1571–1579.
20. Nepper-Christensen L, Lønborg J, Høfsten DE, et al. Benefit from reperfusion with primary percutaneous coronary intervention beyond 12 hours of symptom duration in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2018;**11**:e006842.
21. Schömig A, Mehilli J, Antoniucci D, et al. Mechanical reperfusion in patients with acute myocardial infarction presenting more than 12 hours from symptom onset: a randomised controlled trial. *JAMA* 2005;**293**:2865–2872.
22. Ndrepepa G, Kastrati A, Mehilli J, Antoniucci D, Schömig A. Mechanical reperfusion and long-term mortality in patients with acute myocardial infarction presenting 12 to 48 hours from onset of symptoms. *JAMA* 2009;**301**:487–488.
23. Hochman JS, Lamas GA, Buller CE, Dzavik V, Reynolds HR, Abramsky SJ, Forman S, Ruzyllo W, Maggioni AP, White H, Sadowski Z, Carvalho AC, Rankin JM, Renkin JP, Steg PG, Mascette AM, Sopko G, Pfisterer ME, Leor J, Fridrich V, Mark DB, Knatterud GL; Occluded Artery Trial Investigators. Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006;**355**:2395–2407.
24. Gierlotka M, Gasior M, Wilczek K, Hawranek M, Szkodzinski J, Paczek P, Lekston A, Kalarus Z, Zembala M, Polonski L. Reperfusion by

primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction within 12 to 24 hours of the onset of symptoms (from a prospective national observational study [PL-ACS]). *Am J Cardiol* 2011;**107**:501–508.

25. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the Management of Acute Myocardial Infarction in Patients Presenting With ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**: 119–177.